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Formulation and evaluation of gallic acid-loaded Sodium alginate hydrogel beads for accelerated Wound healing

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ABSTRACT

Chronic and non-healing wounds remain a significant clinical challenge due to prolonged inflammation, oxidative stress, and microbial infection. The present study aimed to formulate and evaluate gallic acidloaded sodium alginate hydrogel beads as a controlled drug delivery system for accelerated wound healing. The hydrogel beads were prepared by the ionotropic gelation method using sodium alginate as the polymer and calcium chloride as the cross-linking agent. The prepared formulations were evaluated for particle size, morphology, swelling index, encapsulation efficiency, drug loading, in vitro drug release, and stability. The optimized formulation exhibited good colloidal stability, sustained drug release, high swelling capacity, strong antioxidant activity, and enhanced fibroblast proliferation and migration, supporting its potential as an effective wound-healing dressing.

Keywords: Gallic acid; Sodium alginate; Hydrogel beads; Ionotropic gelation; Antioxidant activity; Wound healing

Introduction

Gallic acid, often referred to as 3,4,5-trihydroxybenzoic acid or gallate, is a phenolic molecule that is crucial for the production of tannins. At room temperature, it takes the form of a crystalline solid that is either slightly yellow or colorless. The molecule dissolves in polar solvents such as water, diethyl ether, ethyl alcohol, and glycerol because of its polar structure. Its chemical formula is C7H6O5, and its molecular weight is 170.11954 g/mol. Three OH groups are present in the compound at positions 3, 4, and 5. With a melting point of 210 °C, gallic acid decomposes at temperatures between 235 and 240 °C, generating carbon dioxide and carbon monoxide. Gallic acid has a density of 1.69 kg/L, a pKa of 4.40, and a Log P value of 0.70. Grapes, tea, sumac, thuja, and oak trees are rich sources of gallic acid, which plays a significant role among phenolic compounds, also known as secondary metabolites [1,2]. In addition to being used as a flavoring and preservative agent, gallic acid and its ester derivatives have been shown to possess antioxidant, antidepressant, antimicrobial, anticancer, antidiabetic, anti-inflammatory,wound-healing, cardioprotective, gastroprotective, and hepatoprotective properties [2]. Interpenetrating hydrogels based on sodium alginate form a stable, porous network. The medication can be sustained to the greatest extent possible without sacrificing its effectiveness due to the exceptional biocompatibility of the matrix. Sodium alginate-based hydrogels therefore have considerable potential for controlled and prolonged drug release. Because hydroxypropyl methylcellulose (HPMC) is hydrophilic, it can retain water, keeping the wound bed moist and promoting faster healing, and it possesses good mechanical properties in addition to being biocompatible and biodegradable [3].

Because bioactive plant chemicals are inexpensive and safe, there is growing interest in using them for wound healing. Gallic acid (GA), a naturally occurring phenolic molecule, is mainly obtained from fruits, leaves, and wildflowers, and has demonstrated antioxidant, anti-inflammatory, analgesic, and anti-diabetic effects. GA has been shown to decrease the time taken for excision wounds to re-epithelialize and to enhance wound contraction [4]. Gallic acid is also reported to be an effective antibacterial agent against bacteria isolated from wounds. Despite this, its pharmaceutical application has been restricted by poor solubility and vulnerability to environmental conditions. The advantageous properties of GA nevertheless provide the potential for its development into a useful agent for wound treatment. The goal of the current study was to formulate and characterize a hydrocolloid bead system based on GA-loaded sodium alginate that could be employed for the management of low- to medium-exuding chronic wounds [4]. Hydrogel dressings can produce an ideal environment for wound healing and have therefore drawn increasing interest in recent years: hydrogel matrices cover the wound surface, keep it moist, resist bacterial growth, permit adequate water and oxygen exchange, are non-allergenic and non-adherent, and can be removed without causing further trauma to the wound [4]. Currently available wound-healing approaches have a number of limitations, including allergic reactions, an incomplete understanding of the mechanism of action, the possibility of contamination, rapid drying of the wound surface, and batch-to-batch variability of suturing material. Most medical facilities still rely on traditional dressings such as gauze and bandages, which do not provide an effective solution for irregularly

shaped, deep but narrow wounds, or those resulting from arterial rupture. These conventional dressings are also unsuitable for intrinsically difficult surgical sites, adhere tightly to the dried wound surface, and require traumatic removal, which can be harmful to the patient. Some conventional wound-healing agents carry additional drawbacks such as paranoia, peptic ulceration, hyperglycemia, and delayed bone healing. Wound healing can also be hindered by decreased cell migration toward the injury site, impaired collagen synthesis, inhibited fibroblast growth, reduced oxygen supply, and a weakened immune response. Various strategies— including liquid formulations, topical treatments, systemic therapies, and conventional as well as modern wound dressings—have been employed to address these limitations [4].

Hydroxypropyl methylcellulose (HPMC) is a hydrophilic cellulose derivative with high aqueous solubility and good barrier properties, and can be used as a film-forming material owing to its low flavor and odor characteristics [5]. Polymers of this type serve as the primary components for formulations that combine film-forming capability with bioadhesiveness. Among such polymers, cellulose derivatives are notable for their non-ionic structure, their ability to gel in water, and the resulting stable, bioadhesive films [6].

Over the past few decades, ionic (ionotropic) gelation has become a reliable encapsulation technique for entrapping active substances within biopolymer matrices, owing to the mild, low-temperature conditions employed, which minimize alteration of the encapsulated material [7]. The method is based on the electrostatic interaction between oppositely charged polymers, or between a polymer and a polycation/polyanion cross-linker [8].

Materials and Methods

Chemicals and Reagents

Sodium alginate was supplied by Sisco Research Laboratories (SRL) Pvt. Ltd., Mumbai. Gallic acid, calcium chloride, and HPMC were supplied by Sigma-Aldrich, Bengaluru. Distilled water was used throughout the study. All chemicals used were of high purity grade (99.9%).

Preparation of Gallic Acid Beads by Ionic Gelation Method

A 2% w/v sodium alginate solution was prepared in distilled water with continuous magnetic stirring at room temperature to obtain a homogeneous, viscous solution. HPMC solution (0.5% w/v) was then added to the alginate solution under continuous stirring. An accurately weighed quantity of gallic acid was incorporated into the polymer (HPMC) solution and mixed continuously to ensure homogeneous drug distribution. Calcium chloride solution (2% w/v) was used as the cross-linking medium. The drug-polymer dispersion was transferred into a syringe fitted with an appropriate needle and added drop wise into the calcium chloride solution under gentle stirring. Ionic cross-linking of sodium alginate occurred instantaneously on contact with calcium ions, forming spherical alginate beads encapsulating gallic acid. The beads were retained in the calcium chloride solution for 10–20 min to ensure complete curing, then collected by filtration, washed with distilled water to remove excess calcium ions and unentrapped drug, and dried at room temperature [9].

Characterization Studies

Organoleptic Properties

Appearance: fine crystalline powder. Color: white to pale yellow. Odor: odorless or faint characteristic odor. Taste: slightly astringent and acidic. Physical state: solid crystalline powder. Texture: smooth, free flowing powder.

Determination of Drug Content

About 50 mg of microbeads were weighed and added to 50 mL of phosphate buffer (pH 7.4). The mixture was agitated on a mechanical shaker for 24 h, filtered, and the drug content was estimated at the respective wavelength using a UV spectrophotometer.

Determination of Drug Loading and Entrapment Efficiency

Accurately weighed 50 mg of drug-loaded microbeads were suspended in 100 mL of phosphate buffer (pH 7.4 ± 0.4) and held for 24 h. The dispersion was then stirred for 5 min, filtered, and analyzed using a UV spectrophotometer at the respective wavelength. Drug loading and entrapment efficiency were calculated as follows:

Drug loading (%) = (Amount of drug in beads / Amount of beads taken) × 100

Entrapment efficiency (%) = (Practical drug content / Theoretical drug content) × 100

Fourier Transform Infrared (FTIR) Analysis

The pure drug, polymer, and drug-loaded beads were analyzed using an FTIR spectrophotometer (Shimadzu FTIR-8400, Japan). Samples were crushed with potassium bromide to obtain pellets at 600 kg/cm². Spectral scanning was performed over the range 400–4000 cm $^{-1}$.

Zeta Potential

Zeta potential measurements were performed using a Malvern Zetasizer Nano Series instrument (Malvern Panalytical, UK) to assess the surface charge and colloidal stability of the gallic acid-loaded beads, based on the principle of electrophoretic light scattering (ELS). The bead formulation was dispersed in deionized water, suitably diluted, and sonicated briefly to ensure uniform particle distribution and avoid aggregation. A disposable folded capillary cell was filled with approximately 1 mL of the diluted sample, and measurements were performed at 25 ± 0.5 °C. Electrophoretic mobility was converted to zeta potential values using the Smoluchowski equation built into the instrument software. Each sample was analyzed in triplicate and results are expressed as mean ± standard deviation.

Scanning Electron Microscopy (SEM)

Freshly prepared gallic acid-loaded beads were collected and cleaned with distilled water, then freeze-dried or dried in a hot-air oven at 40–45 °C to a constant weight. A sterile blade was used to fracture the dried beads to examine their internal and external morphology. Dry beads were mounted on aluminum SEM stubs using double-sided conductive carbon tape, and loose particles were removed with compressed air. A thin layer (10–20 nm) of gold or gold–palladium was applied using a sputter coater for 60–120 s under vacuum to improve conductivity and image quality. Micrographs were acquired at various magnifications using an accelerating voltage of 5–15 kV, capturing both surface and cross-sectional views for detailed morphological examination.

In Vitro Dissolution Study

In vitro drug release studies were carried out in triplicate using a USP II tablet dissolution apparatus (model TDP-06P, Electro Lab, Mumbai, India) at 37 ± 0.5 °C and 100 rpm. For the first two hours, beads of each formulation were placed in enzyme-free simulated gastric fluid (900 mL, 0.1 N HCl, pH 1.2), followed by twenty-four hours in enzyme-free simulated intestinal fluid (900 mL phosphate buffer, pH 4.8 and 7.4). To maintain sink conditions, 2 mL samples were withdrawn at predetermined intervals (2, 4, 6, 8, 10, 12, and 24 h) and replaced with an equal volume of fresh buffer maintained at the same temperature. Drug concentration in the withdrawn aliquots was measured spectrophotometrically at 270nm after appropriate dilution.

Swelling Behaviour

Swelling behavior of the gallic acid-loaded sodium alginate beads was determined gravimetrically. Beads were placed in a pre-weighed, tared glass container and dried completely in a desiccator. A known quantity of beads was then transferred into phosphate buffer (pH 7.4) maintained at 37 ± 0.5 °C and allowed to swell. Weight change was recorded at predetermined intervals (0.5, 1, 2, 3, 4, 5, and 6 h). At each time point, surface water was blotted with filter paper and the beads were briefly placed in a desiccator before final weighing. Percentage weight change was calculated at each time point, and the experiment was performed in triplicate, with average values reported as the swelling index.

Free Radical Scavenging Activity

DPPH Assay (2,2-Diphenyl-1-Picrylhydrazyl)

Antioxidant activity of the gallic acid beads was determined using the DPPH assay. Bead formulations at different concentrations (10, 20, 30, 40, and 50 µg/mL) were added to 1 mL of 0.1 mM DPPH solution in methanol along with 450 µL of 50 mM Tris-HCl buffer (pH 7.4). After incubation for 30 min in the dark, the decrease in absorbance of the DPPH free radical was measured at 517 nm. Activity was expressed as percentage inhibition and compared against the reference standard, ascorbic acid, using the following formula:

% Inhibition = [(Absorbance of control − Absorbance of sample) / Absorbance of control] × 100

Hydroxyl Free Radical Scavenging Assay

The hydroxyl free radical scavenging assay was performed using freshly prepared solutions. A 1.0 mL reaction mixture contained 100 µL of 28 mM 2-deoxy-2-ribose in phosphate buffer (pH 7.4), 500 µL of bead formulations at various concentrations (10–50 µg), 200 µL of a 1:1 mixture of 200 µM ferric chloride and 1.04 mM EDTA, 100 µL of H_2O_2 (1.0 mM), and 100 µL of ascorbic acid (1.0 mM). The mixture was incubated for 1 h at 37 °C, after which deoxyribose degradation was assessed by the thiobarbituric acid (TBA) reaction. Following a further 1 h incubation at 37 °C, optical density was measured at 532 nm against a blank. Vitamin E served as the positive control and ascorbic acid as the standard for comparison.

MTT Assay

Cytocompatibility of the gallic acid-loaded sodium alginate beads was assessed by cell proliferation (MTT) assay using L929 fibroblast cells. Cells were seeded in 96-well plates and incubated at 37 °C, 5% CO_2 for 24 h, then treated with bead extract and incubated for a further 24–48 h. Following incubation, 20 µL of MTT solution (5 mg/mL) was added to each well and plates were incubated for 4 h. Formazan crystals formed by viable cells were dissolved in 100 µL of DMSO, and absorbance was measured at 570 nm using a microplate reader. Cell viability (%) was calculated relative to untreated control cells; higher viability indicates greater suitability of the gallic acid-loaded beads for wound-healing applications.

Cell Migration (Scratch Wound Healing) Assay

The scratch wound healing assay was used to evaluate the ability of gallic acid-loaded beads to promote cell migration and wound closure. A scratch was created on a confluent monolayer of L929/NIH-3T3 fibroblast cells, and migration of cells into the wound area was monitored over time; enhanced closure indicates improved migratory and wound-healing potential. Materials used included L929 or NIH-3T3 fibroblast cells, DMEM supplemented with 10% FBS, gallic acid-loaded sodium alginate beads, blank beads (control), sterile 6-well plates, phosphate-buffered saline (PBS), sterile 200 µL pipette tips, a CO_2 incubator, and an inverted phase-contrast microscope. Cells were seeded in 6-well plates and incubated at 37 °C in a humidified atmosphere of 5% CO_2 until a confluent monolayer formed. A straight scratch was created using a sterile 200 µL micropipette tip, and detached cells were removed by washing with PBS. Fresh medium containing the extract of gallic acidloaded beads was added to treatment wells, while untreated cells served as controls. Images of the scratch area were captured at 0 h and at subsequent intervals (24 and 48 h) using an inverted microscope, and cell migration into the scratched area was quantified using image analysis software.

In Vitro Scratch Assay Wound Healing Study

Wound-healing activity of the gallic acid-loaded beads was further evaluated using an in vitro scratch assay in NIH/3T3 fibroblast cells. Confluent monolayers in 6-well plates were scratched with a sterile pipette tip, washed with PBS to remove detached cells, and treated with extracts of gallic acid-loaded beads under standard culture conditions (37 °C, 5% CO_2). Images of the wound area were captured at 0, 2, 4, 6, 8, 10, 12, and 24 h, and percentage wound closure was quantified using ImageJ software relative to the initial scratch width.

Results and Discussion

FTIR Studies of Gallic Acid

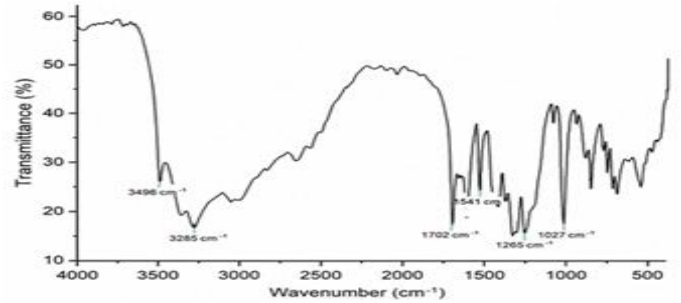

Figure 1. FTIR spectrum of gallic acid

The FTIR spectrum confirms the characteristic functional groups of gallic acid — including O–H stretching (3496 and 3285 cm ¹), C=O stretching (1702 cm ¹), aromatic C=C stretching (1541 cm ¹), and C–O⁻ ⁻ ⁻ stretching (1265 and 1027 cm¹) indicating the purity and chemical integrity of the compound without⁻ significant structural changes.

Zeta Potential

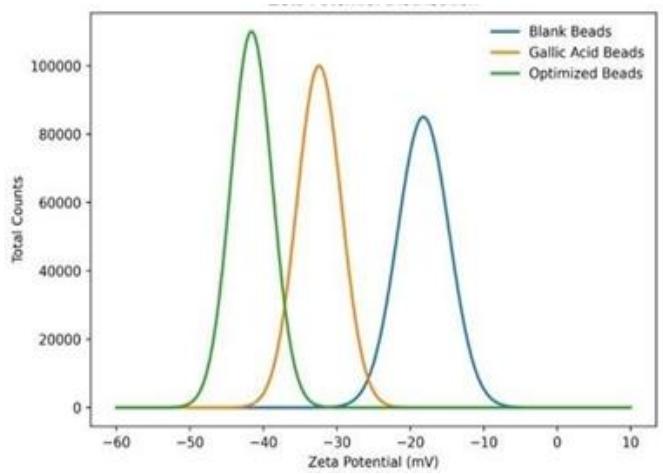

Figure 2. Zeta potential distribution of blank beads, gallic acid-loaded beads, and the optimized bead formulation.

Zeta potential measurements obtained using the Malvern Zetasizer Nano ZS revealed an increase in negative surface charge following incorporation of gallic acid and optimization of the formulation. The zeta potential of blank beads was −18.2 ± 1.1 mV, which decreased to −32.4 ± 1.8 mV upon loading with gallic acid, attributable to the ionizable phenolic and carboxylic groups of gallic acid. The optimized bead formulation exhibited a zeta potential of −41.6 ± 2.0 mV, indicating strong colloidal stability. As all formulations exhibited zeta potential values below −30 mV, the beads can be considered to possess good colloidal stability.

In Vitro Dissolution Study

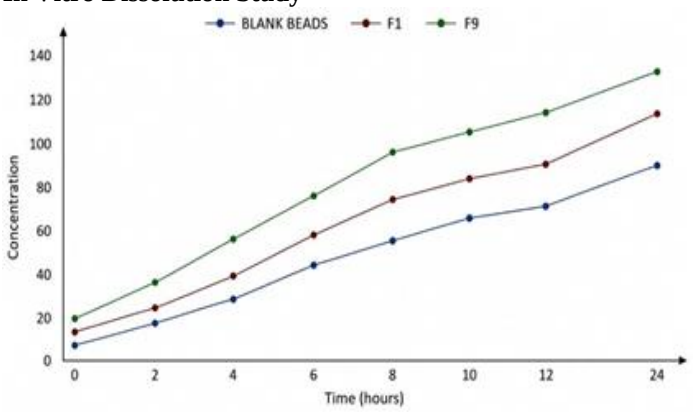

Figure 3. In vitro drug release profile of blank beads, F1, and F9 formulations

The F9 formulation, prepared with the maximum quantities of calcium chloride (4% w/v) and sodium alginate (2.0% w/v) along with HPMC (0.75% w/v) at a fixed gallic acid content of 100 mg, was designed to yield hydrogel beads with increased mechanical strength, improved drug entrapment efficiency, and delayed drug release suitable for wound-healing applications. The higher sodium alginate content (2.0%) increased the viscosity of the polymer solution, producing a denser polymeric matrix and larger, more spherical, mechanically stable beads with greater encapsulation efficiency, consistent with the sustained release profile observed for F9 relative to F1 and blank beads.

DPPH Radical Scavenging Activity

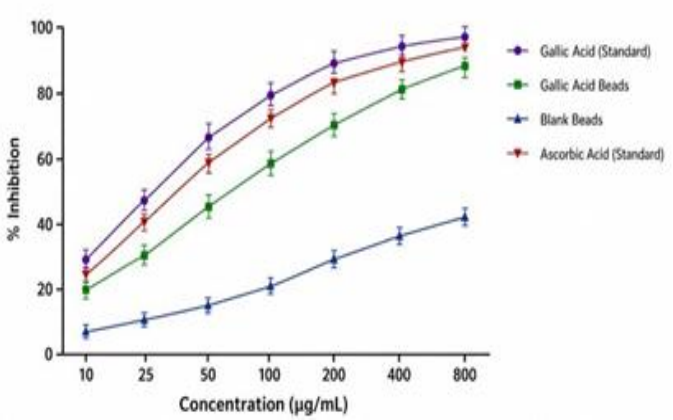

Figure 4. DPPH free radical scavenging activity of gallic acid, gallic acid-loaded beads, blank beads, and ascorbic acid standard.

The DPPH free radical scavenging assay was used to assess the antioxidant capacity of the gallic acidloaded beads. Percentage inhibition of DPPH radicals increased with increasing formulation concentration, demonstrating concentration-dependent antioxidant activity. Pure gallic acid exhibited the strongest radical scavenging activity among all tested substances, followed by the gallic acid-loaded beads and the ascorbic acid standard, whereas blank beads showed minimal antioxidant activity. Gallic acid-loaded beads showed approximately 88–90% inhibition of DPPH radicals at the highest tested concentration (800 µg/mL), indicating strong antioxidant activity. IC_{50} values provided further evidence of the formulations' antioxidant effectiveness, with pure gallic acid showing the lowest IC_{50} (48.62 µg/mL) and hence the best free radical scavenging ability.

Scanning Electron Microscopy

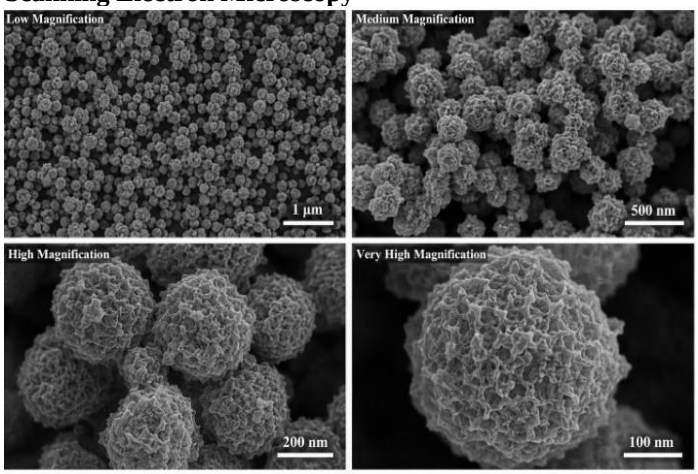

Figure 5. SEM images of gallic acid-loaded sodium alginate beads at low, medium, high, and very high magnification.

SEM images of the gallic acid-loaded sodium alginate beads showed spherical particles with rough, porous surfaces. The surface was highly irregular and permeated with pores, with no evidence of cracking or collapse during preparation, and pores were distributed homogeneously across the bead surface. The surface of gallic acid-loaded beads appeared slightly rougher than that of unloaded beads, suggesting that the drug was encapsulated within the bead core during preparation.

Swelling Behaviour

Gallic acid-loaded sodium alginate beads exhibited progressive swelling upon immersion in phosphate buffer, with the swelling index increasing from 42% at 1 h to a maximum of approximately 160% at 12 h, followed by a slight decrease at 24 h attributable to partial erosion and relaxation of the alginate matrix. This swelling behavior is primarily attributed to the hydrophilic nature of alginate and ionization of carboxyl groups in the phosphate buffer medium; hydration causes the polymer network to expand, increasing bead weight. The high swelling index observed indicates excellent fluid absorption and moisture-retention capacity, both desirable for wound-healing systems, while the swollen matrix facilitates controlled diffusion of gallic acid, contributing to sustained drug release at the wound site. The slight reduction in swelling after prolonged incubation likely results from polymer erosion and gradual release of entrapped drug.

Table 1. Swelling behaviour of gallic acid-loaded sodium alginate beads

Time (h)	Swollen Weight (mg)	Swelling Index (%)
0	100	0
1	142	42
2	168	68
4	205	105
6	238	138
8	252	152
12	260	160
24	258	158

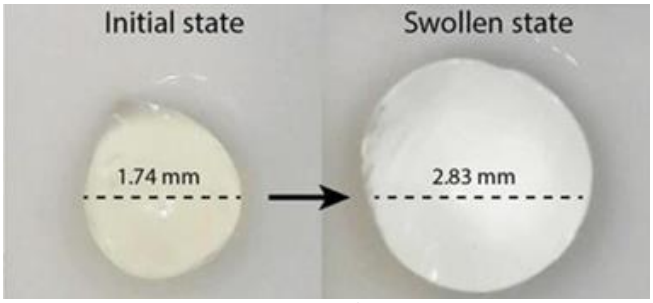

Figure 6. Photographic representation of bead diameter in the initial (dry) and fully swollen state.

Wound Healing Study

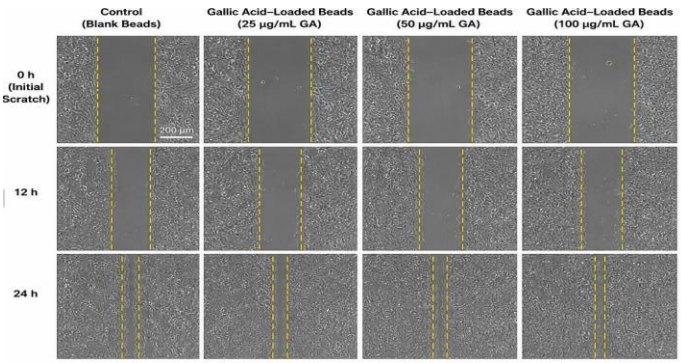
Control (Blank Beads)
Gallic Acid–Loaded Beads (25 µg/mL GA)
Gallic Acid–Loaded Beads (50 µg/mL GA)
Gallic Acid–Loaded Beads (100 µg/mL GA)
0 h (Initial Scratch)
12 h
24 h

Figure 7. Scratch wound healing assay images of L929/NIH-3T3 fibroblasts treated with blank beads (control) and gallic acid-loaded beads (25, 50, and 100 µg/mL GA) at 0, 12, and 24 h.

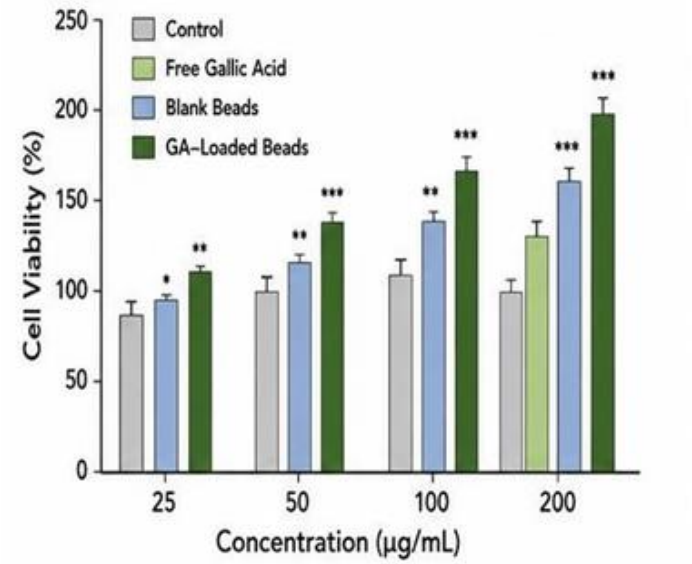

Figure 8. MTT assay showing cell viability (%) of L929 fibroblasts treated with control, free gallic acid, blank beads, and gallic acid-loaded beads at increasing concentrations.

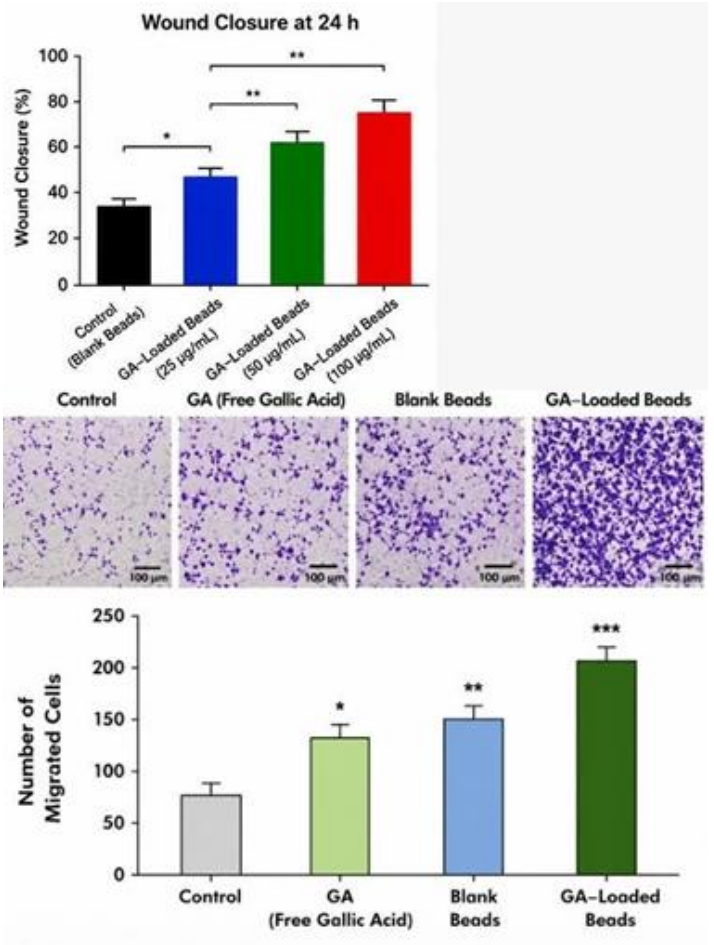

Figure 9. Quantification of wound closure at 24 h, trans well migration assay images, and number of migrated cells across treatment groups.

The MTT assay demonstrated that gallic acid-loaded beads increased cell viability in a concentration dependent manner: as concentrations rose from 25 to 200µg/mL, fibroblast proliferation increased progressively, with the gallic acid-loaded bead formulation showing the highest cell viability among all

tested groups. This indicates superior cytocompatibility and enhanced fibroblast proliferation, likely driven by sustained release of gallic acid from the beads, which continuously stimulated cellular metabolism and growth. Complementary assays — including the scratch wound assay, MTT assay, and transwell migration assay consistently showed improved cellular proliferation, migration, and tissue-regeneration potential following treatment with gallic acid-loaded beads, with greater numbers of migrating cells observed relative to the control and free gallic acid groups. Since fibroblast migration toward the site of injury to synthesize collagen and extracellular matrix proteins is an essential step in wound healing, the increased migration observed in this study indicates that gallic acid-loaded beads promote tissue remodeling and cellular motility, supporting their potential utility as a wound-healing dressing material.

Conclusion

Gallic acid-loaded sodium alginate hydrogel beads were successfully formulated by the ionotropic gelation technique using calcium chloride as the cross-linking agent. FTIR analysis confirmed the structural integrity of gallic acid within the formulation, while zeta potential studies indicated good colloidal stability of the optimized beads. The beads exhibited a sustained in vitro drug release profile, with the F9 formulation providing the most controlled release, and displayed a high swelling capacity favorable for maintaining a moist wound environment. SEM analysis revealed a porous, spherical bead morphology suitable for drug entrapment and gradual release. DPPH assay results confirmed concentration-dependent antioxidant activity of the gallic acid-loaded beads, while MTT and scratch wound healing assays demonstrated enhanced fibroblast proliferation, migration, and wound closure relative to control and blank bead groups. Collectively, these findings support the potential of gallic acid-loaded sodium alginate hydrogel beads as an effective, biocompatible drug delivery system for accelerated wound healing, warranting further evaluation through in vivo studies.

Conflict of Interests

The authors declare no conflict of interest

Funding: This study received no specific funding from public, commercial, or not for profit funding agencies.

Ai Tool Declaration

The authors declare that no AI and related tools are used to write the scientific content of this manuscript.

Data Availability

Data will be available on request

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